Alert for Healthcare Professionals

Duloxetine hydrochloride (marketed as Cymbalta)

FDA Alert [06/05]: Suicidality in Pediatric and Adult Patients

All patients being treated with any type of antidepressants should be observed closely for clinical worsening and suicidality especially during the first few months of therapy and when the dose is modified.

Pediatrics

FDA has concluded that suicidal thinking or behavior may increase in pediatric patients treated with any type of antidepressant, especially early in treatment. Increases in suicidal thinking or behavior due to drug can be expected in about 1 out of 50 treated pediatric patients. Note that, although Cymbalta is prescribed for pediatric patients, it is not approved by FDA for use in pediatric patients.

Adults

Several recent scientific publications report the possibility of an increased risk for suicidal behavior in adults who are being treated with antidepressant medications. Even before these reports became available, FDA began a complete review of all available data to determine whether there is an increased risk of suicidality (suicidal thinking or behavior) in adults being treated with any type of antidepressant medication. It is expected that this review will require a year or longer to complete. In the meantime, FDA is highlighting that adults being treated with any type of antidepressant medication, particularly those being treated for depression, should be watched closely for worsening of depression and for increased suicidal thinking or behavior.

A higher than expected rate of suicide attempts was observed in the open-label extensions of controlled studies of Cymbalta for stress urinary incontinence (SUI) in adult women. An increased rate of suicidality was not seen in controlled trials of Cymbalta for treatment of depression or diabetic neuropathic pain (the approved indications for Cymbalta). Cymbalta is not approved for the treatment of SUI. The FDA is evaluating additional data to determine the relationship, if any, between suicidality and Cymbalta use.

This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of Cymbalta, please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm

Recommendations

All patients being treated with any type of antidepressant for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. For pediatric patients, such observation would generally include at least weekly face-

to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits. Adults whose symptoms worsen while being treated with antidepressant medications, including an increase in suicidal thinking or behavior, should be evaluated by their healthcare professional.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Physicians who are considering prescribing Cymbalta for SUI should consider the following:

- Cymbalta is not approved for the treatment of SUI.
- In the open-label extensions of controlled studies of women with SUI, a higher than expected rate of suicide attempts was observed. A causal relationship with Cymbalta has not been established.

Cymbalta is approved for the treatment of major depressive disorder and diabetic neuropathic pain.

Data Summary

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4 percent, twice the placebo risk of 2 percent. No suicides occurred in these trials; however, the duration of treatment was limited. Spontaneous post-marketing reports of suicide-related events associated with the use of SSRIs, including suicidal ideation, suicide attempt, self-mutilation and completed suicide have been received. Because these events may also be related to underlying psychiatric illness, definitive evaluation of the effects of SSRIs on suicide related events from post-marketing reports alone is not possible, and the data from controlled clinical trials is more informative.

Although there are no similar comprehensive data linking the use of antidepressant medications and an increased risk of suicidality in adults, FDA has initiated a complete review of all available data. FDA has asked the manufacturers of all marketed antidepressants to identify all placebo-controlled clinical trials conducted in adults in their development programs for their

antidepressant products, regardless of the indication studied, and to provide information from these trials to FDA. Manufacturers are being asked to use a similar approach to assembling this information as was used in evaluating the risk of suicidality in placebo-controlled trials in pediatric patients treated with antidepressant medications.

As of June, 2005, in trials of Cymbalta for the treatment of SUI in women who were mostly middle-aged, eleven suicide attempts and three cases of suicidal ideation were reported. The reports of suicide attempt were all from the open label extensions of these placebo-controlled trials (i.e., when all patients were taking Cymbalta). The reports of suicidal ideation occurred both during the placebo-controlled and open label phases of the trials. There was no difference between drug and placebo in the rate of suicidal ideation.

The role of confounding psychosocial stressors or concomitant depression in the cases observed is not clear. The suicide attempt rate in the SUI study population (based on 9,400 patients) was calculated to be 400 per 100,000 person years. This rate is greater than the suicide attempt rate among middle-aged U.S. women that has been reported in published studies, i.e., 150 to 160 per 100,000 person years.

In addition, one death from suicide was reported in a Cymbalta clinical pharmacology study in a healthy female volunteer without SUI. No increase in suicidality was reported in controlled trials of Cymbalta for depression or diabetic neuropathic pain.

Approved Product Labeling
http://www.fda.gov/cder/foi/label/
Additional Information
http://www.fda.gov/cder/drug/antidepressants/default.htm
FDA Patient Information Sheet